

Ms. Sheryl Reilly
Biopesticides and Pollution Prevention Division (7511C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard,
2777 S. Crystal Dr.,
Alexandria, VA 22202

Attn: Shanaz Bacchus

December 22, 2008

Subject: Registration application for BCS Cry2Ae cotton event GHB119 cotton. Active ingredient Bacillus thuringiensis Cry2Ae protein and the genetic material necessary for its production (pTEM12)

EPA CODE B800 and secondary action

#### Dear Ms. Bacchus:

Bayer CropScience (BCS) respectfully submits this registration application for the active ingredient *Bacillus thuringiensis* Cry2Ae protein and the genetic material necessary for its production in event GHB119 cotton plants under section 3 of the Federal Insecticide, Fungicide and Rodenticide Act. The *Bacillus thuringiensis* Cry2Ae protein and the genetic material necessary for its production in event GHB119 cotton plants is covered by a temporary exemption from the requirement of a tolerance issued under 40 CFR 174.530 for the *Bacillus thuringiensis* Cry2Ae protein in cotton.

With this letter and enclosed materials, BCS is applying for a registration of Cry2Ae cotton event GHB119 and a secondary action to register the combined event Cry1Ab x Cry2Ae cotton, produced by conventional breeding. BCS does not intend to offer the individual Cry2Ae cotton event GHB119 product for sale. BCS intends to produce commercially a cotton line called TwinLink<sup>TM</sup> cotton, obtained by conventional breeding of the Cry1Ab cotton event T304-40 and the Cry2Ae cotton event GHB119. A registration application for the Cry1Ab cotton is being submitted concurrently in a separate application.

Bayer CropScience (BCS) has developed cotton [Gossypium hirsutum] plants that express an insecticidal protein, Cry2Ae, from a common soil bacterium, Bacillus thuringiensis (B.t.) subsp. dakota. The Cry2Ae protein is effective in controlling lepidopteran larvae such as bollworm (CBW, Helicoverpa zea), tobacco budworm (TBW, Heliothis virenscens) larvae and fall armyworm (FAW, Spodoptera frugiperda) which are common pests of cotton. These pests cause severe economic damage to the cotton crop if not controlled. If controlled by chemical pesticides, there is the need for a large input annually to control these pests. These plants also contain herbicide tolerant inert ingredient as a selectable marker, the phosphinothricin acetyltransferase (PAT) protein that confers tolerance to glufosinate-ammonium herbicides. Small scale field trial experiments of cotton expressing Cry2Ae protein have shown the plant's ability to protect itself against these pests. This cotton line has been field tested in small scale filed trial experiments, conducted under notifications granted by the U.S. Department of Agriculture's Animal and Plant



Health Inspection Service (APHIS). An Experimental Use Permit 264-EUP-143 has been granted for these products in 2008.

Transgenic cotton plants expressing Cry2Ae protein will provide an excellent addition to grower's options for insect control that reduces or eliminates the need for other insecticide inputs and fills well within an integrated pest management program. Cry2Ae is a *B.t.* insecticidal protein with many of the common characteristics of Cry proteins, with which the Agency is farginar, but has not been used in commercial cotton as a Plant Incorporated Protectant (PIP).

The *cry2ae* gene was isolated from *B.t. dakota* and its DNA sequence was modified for expression in plants. The sequence of the encoded protein confirms that it corresponds to an insecticidal crystal protein, like others used worldwide.

This application contains three copies of the following required information, as defined in EPA form 8570-1, and five copies of draft labeling.

Volume I

Cover letter (this letter)
Transmittal document
Application for Pesticide Registration (EPA Form 8570-1)
Certification with Respect to Citation of Data (EPA Form 8570-34)
Confidential Statement of Formula (EPA Form 8570-4)
Proposed label
Confidentiality classification
Data matrix
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Volume II

Product Characterization of Cry2Ae cotton event GHB119

Volume III

Product Characterization - Nutritional Characterization

Volume IV

Protein Expression Analysis

Volume V

Analyses of Raw Agricultural Commodity

Volume VI

Structural and Functional Equivalence of Cry2Ae and PAT/bar Proteins Produced in bacteria and plant

Volume VII

ORF Analysis - Toxicology (human health assessment)

Volume VIII

Cry2Ae protein: In vitro digestibility study in simulated intestinal fluid.

Volume IX

Cry2Ae Protein With Transit Peptide Epitope Homology And N-Glycosylation Searches.

Volume X



Cry2Ae Protein With Transit Peptide Overall Amino Acid Sequence Homology Search With Known Toxins and Allergens.

Volume XI

Update on Cry2Ae protein: In vitro digestibility study in human simulated gastric fluid overall amino acid sequence homology search with known toxins and allergens, and epitope homology and N-glycosylation searches- supplemental

Volume XII

Cry2Ae Protein: Heat Stability study.

Volume XIII

Toxicology (Human Health Assessment): History of Safe Use History of Safe Use.

Volume XIV

Summary of Non-Target Organism Testing.

Volume XV

Honey Bee

Volume XVI

Ladybug

Volume XVII

Green Lacewing

Volume XVIII

Collembola

Volume XIX

Earthworms

Volume XX

Water Fleas -Daphnia magna

Volume XXI

Bioassay to Determine the DT50 of the Cry2Ae Protein Produced from *Bacillus thuringiensis* after Aerobic Soil Degradation.

Volume XXII

Efficacy Assessment (Field and Laboratory)

Volume XXIII

Waiver from the Requirement to Prepare a Public Interest Document.

Volume XXIV

Waiver from the Requirement to Develop an Insect Resistance Management Plan.

Volume XXV

Detection Methods - rt PCR.

Volume XXVI

Detection Methods - LFS.



Volume XXVII

Detection Methods – ELISA.

Marketing information contained in Volume XIV, has been marked Confidential Business Information. BCS must keep this information confidential to maintain its competitive position in a highly competitive market. Disclosure of this information would cause substantial competitive harm to BCS by allowing other companies to unfairly compete. Information claimed confidential has been removed to a confidential appendix and is cited by cross reference number in the body of this volume.

This application is being concurrent with a request for a permanent exemption from the requirement of a tolerance for *Bacillus thuringiensis* Cry2Ae insecticidal protein and the genetic material necessary for its production in or on all raw agricultural commodities.

BCS respectfully requests that BPPD evaluate this application in time to grant a registration January 1, 2010. We request that this submission is processed concurrently to the Cry1Ab cotton submission as the commercial product is dependent on both registrations.

Please do not hesitate to contact me at (919) 549 2159, or FAX: (919) 549 3929 or Email: ali.scott@bayercropscience.com

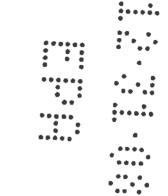
Sincerely,

Ali Scott Ph.D.

Manager, Regulatory Affairs Region Americas



Bayer CropScience BCS Cry2Ae Cotton Section 3 Application Transmittal Document, Page 1 of 7



## TRANSMITTAL DOCUMENT

### SUBMITTED BY

Bayer CropScience LP- BioScience P.O. Box 12014 2 T.W. Alexander Dr. Research Triangle Park, NC 27709

### REGULATORY ACTION IN SUPPORT OF WHICH THIS PACKAGE IS SUBMITTED

Section 3 Registration Request for Bacillus thuringiensis subsp. dakota Cry2Ae Insecticidal Protein (including proteins Cry2Ae and PAT)

### DATE

December 22, 2008

### Author:

Alejandra (Ali) Scott, Ph.D Regulatory Affairs Manager, Region Americas

Total pages 1 of 7





### LIST OF SUBMITTED DOCUMENTS

volume (	<ul> <li>Cover letter</li> <li>Transmittal document</li> <li>Application for Pesticide Registration (EPA Form 8570-1)</li> <li>Certification with Respect to Citation of Data (EPA Form</li> <li>Confidential Statement of Formula (EPA Form 8570-4)</li> <li>Proposed label</li> <li>Confidentiality classification</li> <li>Data matrix</li> <li>Data matrix blacked out</li> </ul>		••••
	MRID Number		•
Volume II	Feruilo, J-M. 2008.  Product Characterization of Cry2Ae cotton event GHB119 Unpublished. Bayer CropScience.	*****	
	MRID Number		•
Volume III	Jesudason, P. 2008.  Product Characterization –Nutritional Characterization of Cupublished. Bayer CropScience.	Cry2Ae Pro	itein
	MRID Number		
Volume IV	Currier, T. 2008.  Protein Expression Analysis of Cotton Event GHB119, Expand PAT/bar Proteins, USA, 2007  Unpublished. Bayer CropScience.	ressing Cr	у2Де
	MRID Number		
Volume V	Martone, A. 2008.  Analyses of Raw Agricultural Commodity (Fuzzy Seed) of Event GHB119 for PAT/bar and Cry2Ae and its Non-transg for PAT/bar and Cry2Ae Proteins.  Unpublished Bayer CropScience.		
	MRID Number		



Bayer CropScience BCS Cry2Ae Cotton Section 3 Application Transmittal Document, Page 3 of 7

Volume VI	Martone, A. 2008.  Structural and Functional Equivalence of Cry2Ae and PAT/bar Proteins Produced in Bacillus thuringiensis (Bt) and Escherichia coli to Cry2Ae a PAT/bar Proteins in GHB119 Cotton, Gossypium hirsutum. Unpublished. Bayer CropScience.	and
	MRID Number	
Volume VII	Capt, A. and Nennstiel, D. 2008.  Toxicology (human health assessment) Summary of analysis of open reading frame homology searches.  Unpublished. Bayer CropScience.	
	MRID Number	••••
Volume VIII	Rouquié, D. 2008.  Cry2Ae Protein In Vitro Digestibility Study In Simulated Intestibal Fluid Unpublished Bayer CropScience.	••••
	MRID Number	••••
Volume IX	Rouquié, D. 2008. Cry2Ae Protein With Transit Peptide Epitope Homology And N-Glycosyl Searches Unpublished. Bayer CropScience.	ation
	MRID Number	
Volume X	Rouquié, D. 2008.  Cry2Ae Protein With Transit Peptide Overall Amino Acid Sequence  Homology Search With Known Toxins and Allergens  Unpublished. Bayer CropScience.	
	MRID Number	



Rouquié, D. 2007.

Volume XI

Bayer CropScience BCS Cry2Ae Cotton Section 3 Application Transmittal Document, Page 4 of 7

	Update on Cry2Ae protein: <i>In vitro</i> digestibility str gastric fluid, overall amino acid sequence homolo toxins and allergens, and epitope homology and N Supplement to MRID 46708905, MRID 46708903 and Unpublished. Bayer CropScience.	gy search with known I-glycosylation search	
	MRID Number	_	
Volume XII	Rouquié, D. 2008. Cry2Ae Protein: Heat Stability study. Unpublished. Bayer CropScience.		
	MRID Number	_ ****	•
Volume XIII	Nennstiel, D. 2008.  Cry2Ae Protein: History of Safe Use Unpublished. Bayer CropScience.	•••••	••••
	MRID Number	_	••••
Volume XIV	Chalmers, A. 2008.  Summary of Non-Target Organism Testing and As  Gossypium hirsutum Transformation event GHB1*  Protein.  Unpublished. Bayer CropScience.		
	MRID Number	_	
Volume XV	Richards, K. 2008.  Evaluation of the Dietary Effect(s) of a Cry2Ae Pro (Apis mellifera L.)  Unpublished Bayer CropScience.	tein on Honey Bee Lar	vae
	MRID Number		



Bayer CropScience BCS Cry2Ae Cotton Section 3 Application Transmittal Document, Page 5 of 7

Volume XVI	Patnaude, M. 2008.  Laboratory Study to Determine the Effects of Cry2Ae (GEM2 Predatory Beetle Coleomegilla maculate Unpublished. Bayer CropScience.	) Protein o	n the
	Robinson, T.; Currier, T.; Chalmers, A.  Analysis of Insect Diet tested in Study EB99X006 Laboratory Determine the Effects of Cry2Ae Protein on the Predatory Be Coleomegilla maculate Unpublished Bayer CropScience		
			•••••
	MRID Number		::
Volume XVII	Patnaude, M. 2009  Cry2Ae protein – Toxicity to Green Lacewing (Chrysoperla re Unpublished. Bayer CropScience.	ufīļabrīs).	
	MRID Number	****	•
Volume XVIII	Patnaude, M. 2008  Chronic Toxicity to Collembola (Folsomia candida) using GE Unpublished. Bayer CropScience.	M2 Protei	ns
	Patnaude, M. 2008 Chronic Toxicity to Collembola (Folsomia candida) using GE (Dose Response). Unpublished Bayer CropScience	M2 Protei	ns
	MRID Number		
Volume XIX	Patnaude, M. 2008.  Cry2Ae Protein - Acute Toxicity to Earthworms (Eisenia fetio Unpublished. Bayer CropScience.	la)	
	MRID Number		



## Bayer CropScience BCS Cry2Ae Cotton Section 3 Application Transmittal Document, Page 6 of 7

Volume XX	Sayers, L. 2008.  Cry2Ae Protein - Ten-Day Toxicity to Water Fleas (Daphi Static Renewal Conditions.  Unpublished. Bayer CropScience.	nia magna) un	der
	MRID Number		
Volume XXI	Martone, A. 2008.  The Use of an Insect Heliothis virescens Bioassay to De the Cry2Ae Protein Produced from Bacillus thuringiensi Degradation.  Unpublished. Bayer CropScience.		
	MRID Number		·.·.
Volume XXII	Jesudason, P. 2008  Cry2Ae: Efficacy Assessment (Field and Laboratory)  Unpublished Bayer CropScience	*****	•
	MRID Number		** *
Volume XXIII	Bushey, D. 2008  Request for Waiver from the Requirement to Prepare a F  Document.  Unpublished. Bayer CropScience	'ublic Interest	
	MRID Number		
Volume XXIV	Bushey, D. 2008  Request for a Waiver from the Requirement to Develop a Management Plan.  Unpublished. Bayer CropScience.	ın Insect Resi	stance
	MRID Number		



Bayer CropScience BCS Cry2Ae Cotton Section 3 Application Transmittal Document, Page 7 of 7

volume XXV	Detection Methods – rt PCR. Unpublished. Bayer CropScience.		
	MRID Number		
Volume XXVI	Nennstiel, D, 2008.  Protein Detection Methods Lateral Flow Strip Unpublished. Bayer CropScience.		••••
	MRID Number		
Volume XXVII	Nennstiel, D, 2008.  Protein Detection Methods Enzyme Linked Immuno Sorbe Unpublished. Bayer CropScience.	nt Assay (El	.ISA)
	MRID Number		

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December 22, 2008

Ali Scott





## UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 1200 Pennsylvania Avenue, N.W. WASHINGTON, D.C. 20460

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and 0.25 hours per response for reregistration and special review activities, including time for comments regarding burden estimate or any other aspect of this collection of information, inc Strategies Division (2822T), U.S. Environmental Protection Agency, 1200 Pennsylvania Ave to this address.	luding suggestions fo	r reducing the burden to: Director, Co	ollection	
Certification with Respect to	Citation of Data			
Applicant's/Registrant's Name, Address, and Telephone Number Bayer CropScience - BioScience. 2 TW Alexander Dr. RTP, NC 27709 (919) 549	2159	EPA Registration Number/File 264-	Symbol	
Active Ingredient(s) and/or representative test compound(s) Cry2Ae protein and the genetic material necessary for its production in cotton eve	nt GHB119	Date December 22, 2008		
General Use Pattern(s) (list all those claimed for this product using 40 CFR Part 15th n/a	8)	Product Name BCS Cry2Ae cotton		
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# DATA MATRIX Date: December 22 2008 Applicant's/Registrant's Name & Bayer CropScience - BioScience Address Address Bayer CropScience - BioScience - BioScience

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
General Application					
	Scott, A. 2008. Administrative Documents. Vol I				
	Cover Letter				
	Transmittal Document			j l	
	Registration Application Form				
	Confidential Statement of Formula (CSF)		264	OWN	
	Proposed Label				
	Confidentiality Classification			]	
	Data Matrix				
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Product Characterization					
	Ferullo, J-M. 2008. Product Characterization of Cry2Ae cotton event		264	OWN	
	GHB119. Vol II			•	
	Jesudason, P. 2008. Product Characterization – Nutritional		264	l own l	
	Characterization of Cry2Ae Protein. Vol III				
	Currier, T. 2008. Protein Expression Analysis of Cotton Event		264	l own l	
	GHB119, Expressing Cry2Ae and PAT/bar Proteins. Vol IV				
	Martone, A. 2008. Analyses of Raw Agricultural Commodity (Fuzzy				
	Seed) of Cry2Ae Cotton Event GHB119 for PAT/bar and Cry2Ae		264	OWN	
	and its Non-transgenic Counterpart for PAT/bar and Cry2Ae				
	Proteins. Vol V			[	

Signature: Au Survio	Name and Title: Ali Scott, Regulatory Affairs Manager	Date: December 22, 2008
EPA Form 8570-35 (9-97) Electronic Paper versions available. Submit only	Paper version. Agend	y Internal Use Copy





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## DATA MATRIX Date: December 22 2008 Applicant's/Registrant's Name & Bayer CropScience - BioScience Address Action Bayer CropScience - BioScience Address 2 T.W. Alexander Drive Research Triangle Park, NC 27709 Ingredient: BCS Cry2Ae as expressed in cotton and the genetic material necessary for its production.

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
	Martone, A. 2008. Structural and Functional Equivalence of Cry2Ae and PAT/bar Proteins Produced in Bacillus thuringiensis (Bt) and Escherichia coli to Cry2Ae and PAT/bar Proteins in GHB119 Cotton, Gossypium hirsutum. Vol VI		264	OWN	
luman Health Assessment				<u> </u>	
(Toxicology data)					
	Capt, A. and Nennstiel, D. 2008. Toxicology (human health assessment) Summary of analysis of open reading frame homology searches. Vol VII		264	OWN	-
	Rouquié, D. 2008. Cry2Ae protein: In vitro digestibility study in simulated intestinal fluid. Vol VIII		264	OWN	
	Rouquié, D. 2008. Cry2Ae Protein With Transit Peptide Epitope Homology And N-Glycosylation Searches. Vol IX		264	OWN	
	Rouquié, D. 2008. Cry2Ae Protein With Transit Peptide Overall Amino Acid Sequence Homology Search With Known Toxins and Allergens. Vol X	_	264	OWN	
	Rouquié, D. 2007. Update on Cry2Ae protein: In vitro digestibility study in human simulated gastric fluid, overall amino acid sequence homology search with known toxins and allergens, and epitope homology and N-glycosylation searches. Supplement to MRID 46708905, MRID 46708903 and MRID 46708904. Vol XI		264	OWN	

Signature: Au Sur Date: December 22, 2008

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# DATA MATRIX Date: December 22 2008 Applicant's/Registrant's Name & Bayer CropScience - BioScience Address 2 T.W. Alexander Drive Research Triangle Park, NC 27709 Ingredient: BCS Cry2Ae as expressed in cotton and the genetic material necessary for its production.

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
	Description of the amino acid sequence of the Cry2Ae protein.	46708902	264	OWN	
	Cry2Ae (GEM2) protein: Overall amino acid sequence homology search with known toxins and allergens.	46708903	264	OWN	
	Cry2Ae (GEM2) protein: Epitope homology and N-glycosylation searches	46708904	264	OWN	
	Cry2Ae (GEM2) protein: In vitro digestibility study in simulated gastric fluid	46708905	264	OWN	
	Cry2Ae (GEM2) protein: Acute toxicity by intravenous injection in the mouse	46708906	264	OWN	
	Analysis to Determine if the Cry2Ae (GEM2) Protein from Cotton Leaves is Glycosylated	46708907	264	OWN	
	Cry2Ae (GEM2) protein: Acute Toxicity by Oral Gavage in Mice	47125102	264	OWN	_
	Rouquié, D. 2008. Cry2Ae Protein: Heat Stability study. Vol XII	<u> </u>	264	OWN	
	Nennstiel, D. 2008. Cry2Ae Protein: History of Safe Use. Vol XIII		264	OWN	
	Phosphinothricin Acetyltransferase (PAT) - bar gene product: Epitope hornology and glycosylation searches.	47076903	264	OWN	
	Phosphinothricin-Acetyl-Transferase (PAT)- bar gene product: Overall amino acid sequence homology search with known toxins and allergens.	46455105	264	OWN	
	Phosphinothricin-Acetyl-Transferase (PAT) - bar gene product: Epitope homology and glycosylation searches	46455106	264	OWN	

Signature: Au Sur Date: December 22, 2008

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# Date: December 22 2008 Applicant's/Registrant's Name & Bayer CropScience - BioScience Address Address Bayer CropScience - BioScience - BioScience

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
	Phosphinothricin-Acetyl-Transferase (PAT) - bar gene product: In vitro digestibility test in simulated gastric fluid	46455107	264	OWN	
	Phosphinothricin-Acetyl-Transferase (PAT) - bar gene product: In vitro digestibility test in simulated intestinal fluid.	46455108	264	OWN	
	PAT (Phosphinothricin-Acetyl-Transferase) protein derived from bar gene: Acute toxicity by intravenous injection in the mouse.	46455109	264	OWN	
	<ul> <li>References-</li> <li>Betz, F.S., Hammond, B.G., Fuchs, R.L. 2000. Safety and advantages of Bacillus thuringiensis-protected plants to control insect pests. Regulatory Toxicol. Pharamacol. 32: 156-173.</li> <li>McClintock, J.T., C.R. Schaffer, Sjoblad, R.D. 1995. A comparative review of the mammalian toxicity of Bacillus thuringiensis-based pesticides. Pestic. Sci. 45: 95-105.</li> <li>Mendelsohn, M., J. Kough, Z. Vaituzis and K. Matthews, 2003. Are B.t. Crops Safe? Nature Biotechnology 21 (9) 1003-1010</li> </ul>	46455110		PL	
Environmental Assessment (Non target data)				-	-
	Chalmers, A. 2008. Summary of Non-Target Organism Testing and Assessment of Risk of Gossypium hirsutum Transformation event GHB119 Expressing Cry2Ae Protein. Vol XIV		264	OWN	
OPPTS 885.4380	Richards, K. 2008. Evaluation of the Dietary Effect(s) of a Cry2Ae Protein on Honey Bee Larvae (Apis mellifera L.) Vol XV		264	OWN	

Signature: Au Surv	Name and Title: Ali Scott, Regulatory Affairs Manager	Date: December 22, 2008

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# Date: December 22 2008 Applicant's/Registrant's Name & Bayer CropScience - BioScience Address 2 T.W. Alexander Drive Research Triangle Park, NC 27709 Ingredient: BCS Cry2Ae as expressed in cotion and the genetic material necessary for its production.

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
OPPTS 885.4340	Patnaude, M. 2008. Laboratory Study to Determine the Effects of GEM2 Protein on the Predatory Beetle Coleomegilla maculate. Vol XVI		264	OWN	
	Robinson, T.; Currier, T.; Chalmers, A. Analysis of Insect Diet tested in Study EB99X006 Laboratory Study to Determine the Effects of Cry2Ae Protein on the Predatory Beetle Coleomegilla maculata. Vol XVI		264	OWN	
OPPTS 885.4340	Patnaude, M. 2009 Cry2Ae protein – Toxicity to Green Lacewing (Chrysoperla rufilabris). Vol XVII		264	OWN	
OPPTS 885,4340	Patnaude, M. Chronic Toxicity to Collembola (Folsomia candida) using GEM2 Proteins. Vol XVIII.		264	OWN	
OPPTS 885.4340	Patnaude, M. Chronic Toxicity to Collembola (Folsomia candida) using GEM2 Proteins (Dose Response). Vol XVIII.		264	OWN	
OPPTS 885.4340	Patnaude, M. 2008 Cry2Ae Protein - Acute Toxicity to Earthworms (Eisenia fetida). Vol XIX		264	OWN	-
OECD Guideline 202 OPPTS 885,4240	Sayers, L. 2008. Cry 2Ae Protein - Ten-Day Toxicity Test to Water Fleas (Daphnia magna) under Static Renewal Conditions. Vol XX		264	OWN	
Environmental fate data				<u></u> '	
	Martone, A. 2008. The Use of an Insect Heliothis virescens Bioassay to Determine the DT50 of the Cry2Ae Protein Produced from Bacillus thuringiensis After Aerobic Soil Degradation. Vol XXI		264	OWN	

ignature: Au Surva	Name and Title: Ali Scott, Regulatory Affairs Manager	Date: December 22, 2008
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# DATA MATRIX Date: December 22 2008 Applicant's/Registrant's Name & Bayer CropScience - BioScience Address Address Address Bayer CropScience - BioScience - BioScience Product: BCS Cry2Ae cotton. Product: BCS Cry2Ae cotton.

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
	<ul> <li>References-</li> <li>Crecchio, C., Stotzky, G. 1998. Insecticidal activity and biodegradation of the toxin from <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> bound to humic acids from soil. Soil Bio. Biochem. 30: 463-470.</li> <li>Donegan, K.K., Seidler, R.J. 1998. Effect of Transgenic Cotton Expressing the <i>Bacillus thuringiensis</i> var <i>kurstaki</i> Endotoxin on Soil Micro-organisms—Risk Assessment Studies. Biotechnology in Agriculture and Forestry, Vol 42 Cotton. Bajaj, Y.P.S. (Ed). Springer-Verlag Berlin Heidelberg.</li> <li>Donegan, K.K., C.J. Palm, V.J. Fieland, L.A. Porteous, L.M. Ganio, D.L. Schaller, L.Q. Bucao, Seidler, R.J. 1995. Changes in levels, species and DNA fingerprints of soil microorganisms associated with cotton expressing the <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> endotoxin. Appl. Soil Ecol. 2:111-124.</li> <li>EPA. 1998a. Reregistration eligibility decision: <i>Bacillus thuringiensis</i>. EPA 783-R-98-004.</li> <li>EPA. 1998b. R.E.D. Facts: <i>Bacillus thuringiensis</i>. EPA 738-F-98-001.</li> <li>IPCS (International Programme on Chemical Safety). 1999. Environmental Health Criteria, 217: <i>Bacillus thuringiensis</i>. http://www.who.int/pcs/ehc/summaries/ehc_217.html</li> <li>Koskella, J., Stotzky, G. 1997. Microbial utilization of free and clay-bound insecticidal toxins from <i>Bacillus thuringiensis</i> and their retention of insecticidal activity after incubation with microbes. Appl. Environ. Microbiol. 63: 3561-3568.</li> <li>Palm, C.J., R.J. Seidler, K.K. Donegan, Hamis, D. 1993. Transgenic plant pesticides: fate and persistence in soil. Plant Physiol. Suppl. 102:166.</li> <li>Palm, C.J., K. Donegan, D. Hamis, Seidler, R.J. 1994. Quantification in soil of <i>Bacillus thuringiensis</i> var. <i>kurstaki</i> delta-endotoxin from transgenic plants. Mol. Ecol. 3: 145-151.</li> <li>Palm, C.J., D.L. Schaller, K.K. Donegan, Seidler, R.J. 1996. Persistence in soil of</li> </ul>	46455112 and 46600910		PL	

Signature: Au Substitute: Ali Scott, Regulatory Affairs Manager Date: December 22, 2008

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Guideline Reference Number	Guideline Study Name	Đ .	MRID Number	Submitter	Status	Note
	<ul> <li>Microbiol. 42: 1258-1262.</li> <li>Pratt, G.E., Royce, L.A., Croft, B.A. 1993. Measurements of toxicity of soils following incorporation of plant residues engineered with <i>Bacillus thuringiensis</i> var <i>kurstaki</i> endotoxin using <i>Heliothis virescens</i> growth bioassay, Proc 5th Investigators Meeting for the EPA's Environmental Release of Biotechnology Research program, College Park, Maryland.</li> <li>Saxena D, Stotzky G. 2000. Insecticidal toxin from <i>Bacillus thuringiensis</i> is released from roots of transgenic <i>B.t.</i> com in vitro and in vivo. FEMS Microbiology Ecology 33: 35-39.</li> <li>Tapp, H., Stotzky, G. 1995. Insecticidal activity of the toxins from <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> and <i>tenebronis</i> adsorbed and bound on pure and soil clays. Appl. Environ. Microbiol. 61: 1786-1790.</li> <li>Tapp, H., Stotzky, G. 1998. Persistence of the insecticidal toxin from <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> in soil. Soil Biol. Biochem. 30: 471-476.</li> <li>Tapp, H., L. Calamai, Stotzky, G. 1994. Adsorption and binding of the insecticidal proteins from <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> and subsp. <i>tenebrionis</i> on clay minerals. Soil Biol Biochem. 26: 663-679.</li> <li>USDA, Forest Service. 1999. <i>Bacillus thuringiensis</i>. Pesticide Fact Sheet Available at <a href="http://iinfoventures.com/e-hith/pestcide/bacillus.html">http://iinfoventures.com/e-hith/pestcide/bacillus.html</a></li> <li>Venkateswerlu, G., G. Stotzky. 1992. Binding of the Protoxin and Toxin Proteins of <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> on Clay Minerals. Curr. Microbiol. 25: 225-2</li> </ul>	SUDMITTEE SUDMITTEE		Status		
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	Jesudason, P. 2008. Cry2Ae: Efficacy Asse Laboratory). Vol XXII	essment (Field and		264	OWN	
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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Insect Resistance Management					
	Bushey, D. 2008. Request for a Waiver from the Requirement to Develop an Insect Resistance Management Plan. Vol XXIV		264	OWN	
Benefits and tools					
	Bushey, D. 2008. Request for Waiver from the Requirement to Prepare a Public Interest Document. Vol XXIII		264	OWN	
	Nennstiel, D, 2008. Detection Methods - rt PCR. Vol XXV		264	OWN	_
-	Nennstiel, D, 2008. Protein Detection Methods Lateral Flow Strip – LFS. Vol XXVI		264	OWN	
	Nennstiel, D, 2008. Protein Detection Methods Enzyme Linked Immuno Sorbent Assay (ELISA). Vol XXVII		264	OWN	
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# DATA MATRIX Date: December 22 2008 Applicant's/Registrant's Name & Bayer CropScience - BioScience Address At Alexander Drive Research Triangle Park, NC 27709 Ingredient: BCS Cry2Ae as expressed in cotton and the genetic material necessary for its production.

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
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Name and Title: Ali Scott, Regulatory Affairs Manager

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Date: December 22 2008

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## DATA MATRIX EPA Reg. No. 264 Page 2 of 8 Bayer CropScience - BioScience Product: BCS Cry2Ae cotton.

Applicant's/Registrant's Name & Bayer CropScience - Bio Address 2 T.W. Alexander Drive

Research Triangle Park, NC 27709

Ingredient: BCS Cry2Ae as expressed in cotton and the genetic material necessary for its production.

**Guideline Study Name MRID** Number Submitter **Guideline Reference Number** Status Note 264 OWN. 264 OWN OWN 264 OWN 264 264 OWN 264 OWN

Signature: Au Suns

Name and Title: Ali Scott, Regulatory Affairs Manager

Date: December 22, 2008

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## DATA MATRIX Date: December 22 2008 Applicant's/Registrant's Name & Bayer CropScience - BioScience Address Address 2 T.W. Alexander Drive Research Triangle Park, NC 27709 Ingredient: BCS Cry2Ae as expressed in cotton and the genetic material necessary for its production.

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
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Name and Title: Ali Scott, Regulatory Affairs Manager

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# DATA MATRIX Date: December 22 2008 Applicant's/Registrant's Name & Bayer CropScience - BioScience Address Address Bayer CropScience - BioScience - BioScience

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
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Name and Title: Ali Scott, Regulatory Affairs Manager

Date: December 22, 2008

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### DATA MATRIX

Date: December 22 2008

Applicant's/Registrant's Name & Bayer CropScience - BioScience Product: BCS Cry2Ae cotton.

Address

2 T.W. Alexander Drive Research Triangle Park, NC 27709

Ingredient: BCS Cry2Ae as expressed in cotton and the genetic material necessary for its production.

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
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Name and Title: Ali Scott, Regulatory Affairs Manager

Date: December 22, 2008

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Name and Title: Ali Scott, Regulatory Affairs Manager

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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
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Proposed label
EPA File Symbol 264 - RNOL
Cotton

## BCS Cry2Ae Cotton INSECT RESISTANT COTTON SEED



Insect-resistant cotton seed that produces an insecticidal protein Cry2Ae from Bacillus thuringiensis. For control of Cotton Bollworm, Tobacco Budworm, Pink Bollworm, Fall Armyworm, and Beet Armyworm

**Active Ingredient:** 

Bacillus thuringiensis Cry2Ae protein and the genetic material necessary for its production (from 

Inert Ingredient:

A substance produced by a herbicide tolerance gene and its controlling sequences 

### **KEEP OUT OF REACH OF CHILDREN** CAUTION

EPA REGISTRATION NUMBER: EPA ESTABLISHMENT NUMBER: 000264-TX-004

Bayer CropScience 2 T.W. Alexander Dr. RTP, NC 27709

<sup>\*</sup> Percent protein on a dry weight basis as expressed in cotton seeds.





It is a violation of federal law to use this product in any manner inconsistent with its labeling.

This plant-incorporated protectant may be combined through conventional breeding with officer registered plant-incorporated protectants that are similarly approved for use in combination, through conventional breeding, with other plant-incorporated protectants to produce inbred cotton varieties with combined pesticidal traits.

No commercial planting of this product is permitted south of Route 60 in Florida. Commercial planting of this product is prohibited in Hawaii, Puerto Rico and the US Virgin Islands.

Bt cotton is not permitted to be planted in the following counties of the Texas panhandle: Dallam, Sherman, Hansford, Ochiltree, Lipscomb, Hartley, Moore, Hutchinson, Roberts and Carlson.

### **USE PATTERN**

CROP	PESTS
Cotton	Cottori Bollworm Tobacco Budworm Pink Bollworm Beet Armyworm

EPA Accepted: \_\_/\_\_/\_\_

Bayer CropScience BCS Cry2Ae Cotton Section 3 Application Confidentiality classification letter, Page 1 of 2

December 22, 2008

Biopesticides and Pollution Prevention Division (7511C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard,
2777 S. Crystal Dr.,
Alexandria, VA 22202

Subject: Registration application for BCS Cry2Ae cotton event GHB119 cotton. Active ingredient *Bacillus thuringiensis* Cry2Ae protein and the genetic material necessary for its production. Confidentiality classifications for Registration application.

The present letter identifies the confidentiality classification for all of the documents supporting this application.

Volume number	Content		fidentiality sification
	Scott, A. 2008. Administrative Documents.		_
	Cover Letter		n/a
	Transmittal Document		n/a
	Registration Application Form		Α
I	<ul> <li>Confidential Statement of Formula (CSF)</li> </ul>		С
	Proposed Label		Α
	Confidentiality Classification		n/a
	Data Matrix		С
	Data Matrix blacked out	•	Α
II	Feruilo, J-M. 2008. Product Characterization of Cry2Ae cotton		В
	event GHB119.		
Ш	Jesudason, P. 2008. Product Characterization – Nutritional	l	В
	Characterization of Cry2Ae Protein.		
IV	Currier, T. 2008. Protein Expression Analysis of Cotton Event	!	В
	GHB119, Expressing Cry2Ae and PAT/bar Proteins.	L	
	Martone, A. 2008. Analyses of Raw Agricultural Commodity		
V	(Fuzzy Seed) of Cry2Ae Cotton Event GHB119 for PAT/bar and		В
•	Cry2Ae and its Non-transgenic Counterpart for PAT/bar and		_
	Cry2Ae Proteins.	ļ	
	Martone, A. 2008. Structural and Functional Equivalence of		
l vi	Cry2Ae and PAT/bar Proteins Produced in Bacillus thuringiensis		В
· · ·	(Bt) and Escherichia coli to Cry2Ae and PAT/bar Proteins in	1	
	GHB119 Cotton, Gossypium hirsutum.		

Capt, A. and Nennstie!, D. 2008. Toxicology (human health assessment) Summary of analysis of open reading frame homology searches.	В
Rouquié, D. 2008. Cry2Ae protein: <i>In vitro</i> digestibility study in simulated intestinal fluid.	В
Rouquié, D. 2008. Cry2Ae Protein With Transit Peptide Epitope Homology And N-Glycosylation Searches.	В
Rouquié, D. 2008. Cry2Ae Protein With Transit Peptide Overall Amino Acid Sequence Hornology Search With Known Toxins and Allergens.	В
Rouquié, D. 2007. Update on Cry2Ae protein: <i>In vitro</i> digestibility study in human simulated gastric fluid, overall amino acid sequence homology search with known toxins and allergens, and epitope homology and N-glycosylation searches.	В
Rouquié, D. 2008. Cry2Ae Protein: Heat Stability study.	В
	В
Chalmers, A. 2008. Summary of Non-Target Organism Testing and Assessment of Risk of Gossypium hirsutum Transformation event GHB119 Expressing Cry2Ae Protein.	В
Richards, K. 2008. Evaluation of the Dietary Effect(s) of a Cry2Ae Protein on Honey Bee Larvae (Apis mellifera L.).	В
Patnaude, M. 2008. Laboratory Study to Determine the Effects of GEM2 Protein on the Predatory Beetle Coleomegilla maculata.	В
Robinson, T.; Currier, T.; Chalmers, A. Analysis of Insect Diet tested in Study EB99X006 Laboratory Study to Determine the Effects of Cry2Ae Protein on the Predatory Beetle Coleomegilla maculata.	В
Patnaude, M. 2008. Cry2Ae Protein. Toxicity to Green Lacewing	В
Patnaude, M. Chronic Toxicity to Collembola (Folsomia candida) using GEM2 Proteins. Patnaude, M. Chronic Toxicity to Collembola (Folsomia candida) using GEM2 Proteins (Dose Response)	В
Patnaude, M. 2008 Cry2Ae Protein - Acute Toxicity to Earthworms (Eisenia fetida)	В
Sayers, L. 2008. Cry2Ae Protein – Теп Day Toxicity Test to Water Fleas ( <i>Daphnia magna</i> ) Under Static-Renewal Conditions.	В
Martone, A. 2008. The Use of an Insect Heliothis virescens Bioassay to Determine the DT50 of the Cry2Ae Protein Produced from Bacillus thuringiensis After Aerobic Soil Degradation.	В
Jesudason, P. 2008. Cry2Ae: Efficacy Assessment (Field and Laboratory).	В
Bushey, D. 2008. Request for Waiver from the Requirement to Prepare a Public Interest Document.	В
Bushey, D. 2008. Request for a Waiver from the Requirement to Develop an Insect Resistance Management Plan.	В
	В
Nennstiel, D, 2008. Detection Methods – LFS.	В
Nennstiel, D, 2008. Detection Methods – ELISA.	В
	assessment) Summary of analysis of open reading frame homology searches. Rouquié, D. 2008. Cry2Ae protein: In vitro digestibility study in simulated intestinal fluid. Rouquié, D. 2008. Cry2Ae Protein With Transit Peptide Epitope Homology And N-Glycosylation Searches. Rouquié, D. 2008. Cry2Ae Protein With Transit Peptide Overall Amino Acid Sequence Homology Search With Known Toxins and Allergens. Rouquié, D. 2007. Update on Cry2Ae protein: In vitro digestibility study in human simulated gastric fluid, overall amino acid sequence homology search with known toxins and allergens, and epitope homology and N-glycosylation searches. Rouquié, D. 2008. Cry2Ae Protein: Heat Stability study. Nennstiel, D. 2008. Cry2Ae Protein: Heat Stability study. Nennstiel, D. 2008. Cry2Ae Protein: History of Safe Use. Chalmers, A. 2008. Summary of Non-Target Organism Testing and Assessment of Risk of Gossypium hirsutum Transformation event GHB119 Expressing Cry2Ae Protein. Richards, K. 2008. Evaluation of the Dietary Effect(s) of a Cry2Ae Protein on Honey Bee Larvae (Apis mellifera L.). Patnaude, M. 2008. Laboratory Study to Determine the Effects of GEM2 Protein on the Predatory Beetle Coleomegilla maculata. Robinson, T.; Currier, T.; Chalmers, A. Analysis of Insect Diet tested in Study EB99X006 Laboratory Study to Determine the Effects of Cry2Ae Protein on the Predatory Beetle Coleomegilla maculata. Patnaude, M. 2008. Cry2Ae Protein. Toxicity to Green Lacewing (Chrysoperia rufliabris). Patnaude, M. Chronic Toxicity to Collembola (Folsomia candida) using GEM2 Proteins. Patnaude, M. Chronic Toxicity to Collembola (Folsomia candida) using GEM2 Proteins (Dose Response) Patnaude, M. Chronic Toxicity to Collembola (Folsomia candida) using GEM2 Proteins (Dose Response) Patnaude, M. 2008. Cry2Ae Protein – Ten Day Toxicity to Earthworms (Eisenia fetida) Sayers, L. 2008. Cry2Ae Protein – Ten Day Toxicity to Earthworms (Eisenia fetida) Sayers, L. 2008. Request for Waiver from the Requirement to Prepare a Public Interest Document. Bushey, D. 2008

